REMARKS

Claims 1, 3-8, 10-14, 16-18, and 20-23 are in the case. Claims 1, 3-8, 10-14, 16-18 and 20-21 have been amended herein. Support for the amendments can be found in the application as filed, specifically in previous claims 1, 2 and 9. Claims 2, 9, 15 and 19 are cancelled. No new matter has been added.

REJECTIONS UNDER 35 U.S.C. § 112 SECOND PARAGRAPH

The Examiner rejected claim 1 under 35 U.S.C. § 112, as lacking proper antecedent basis for "injured site". Claim 1 was corrected to replace term "the" by "an".

REJECTION UNDER 35 U.S.C. § 102(b)

The Examiner rejected claims 1, 8-9, 14 and 18-19 as being anticipated by U.S. Patent No. 5,866,561 to Mark T. Ungs ("Ungs") under 35 U.S.C. § 102(b).

The Examiner noted that the recitation "for improving reendothelization and vascular endothelial function" in claim 1 has not been given patentable weight because this recitation occurs in the preamble.

Claim 1 has been reformulated to recite a step of improving reendothelization and vascular endothelial function by the administration of estradiol. Amended claim 1 further recites that the administration is performed with a device and recites a dosage.

Never does Ungs disclose or suggest improving reendothelization and vascular function at an injured site of a vessel by administering estradiol and never does it disclose or suggest a specific dosage for *in situ* administration of estradiol.

For the above reasons, Ungs fails to anticipate the claimed invention. Accordingly, the Examiner is respectfully requested to reconsider and withdraw this rejection.

REJECTION UNDER 35 U.S.C. § 103 (a)

Claims 12-13 and 22-23 have been rejected as being obvious over Ungs under 35 U.S.C. § 103 (a). Claims 2-4 and 15-17 have been rejected as being obvious over Ungs under 35 U.S.C. § 103 (a) in view of Collins. Claims 5-7, 10-11 and 20-21 have been rejected as being obvious over Ungs under 35 U.S.C. § 103 (a) in view of U.S. Patent No. 4,727,064 to Josef Pitha ("Pitha").

Applicant respectfully disagrees and submits that even if Ungs had suggested that estradiol could be used to reduce smooth muscle cell proliferation or to reduce their migration, it would not make the present claims obvious.

The Applicant is the first to demonstrate that estradiol can be used locally to repair vessels i.e. improve reendothelization and vascular endothelial function in a vessel of a mammal in need for repair. To the Applicant's knowledge, the Applicant is the first to have actually applied estradiol with a device at the injured site of a vessel of an animal for any purpose whatsoever, be it for improving reendothelization or for inhibiting restenosis. It is submitted that the advantageous effect of this compound on vascular reendothelization and vascular function could not be predicted.

Indeed, substances able to inhibit smooth muscle cell proliferation or migration do not systematically also improve reendothelialization or vascular function. These events are independent events that are affected differently by different compounds. Hence, paclitaxel and sirolimus are drugs known to play a role only on the inhibition of the proliferation of smooth muscle cells. They do not improve reendothelialization or vascular function as is apparent from the attached following articles: Suzuki *et al.*; Sousa *et al.*; Hiatt *et al*; Drachman *et al.*; Johnson & Johnson technical document on Sirolimus; and Boston Scientific technical document on paclitaxel.

The Examiner is again referred to Dr. Stack's previously submitted Declaration paragraphs 11-14 (see Applicant's response dated January 19, 2006) as further support of the non obviousness of the present invention:

> "Very few agents are known to promote blood vessel wall repair. In fact, until recently, very few appreciated the usefulness of regenerating the endothelium. On the contrary, many believed in a toxic approach such as brachytherapy to kill smooth muscle cells and avoid the endothelium to repair.
>
> It is my experience that it cannot be predicted whether an agent known to prevent or reduce smooth muscle cell proliferation and/or to prevent or reduce blood vessel wall thickening will also promote reendothelization.
>
> Indeed, substances able to inhibit smooth muscle cell proliferation or migration do not systematically also improve reendothelialization or vascular function. Hence paclitaxel and sirolimus are anti-proliferative agents that do not promote reendothelization.
>
> In my opinion therefore, the knowledge that beta-estradiol had an ability to reduce smooth muscle cell proliferation was not sufficient, for someone skilled in the art, to predict that beta-estradiol could also promote reendothelization and endothelial function."

It is further submitted that estradiol's reported *in vitro* effects on vascular smooth muscle cell proliferation and/or migration were not predictive of any of its effect at the injured site of a vessel *in vivo*. In fact, even estradiol's reported *in vitro* effects on vascular smooth muscle cells were inconsistent prior to the Applicant's invention as recognized by Dai Do et al. (submitted in IDS dated July 15, 2002) "Experiments with cultured vascular smooth muscle cells obtained from rats and pigs, however revealed inconsistent antiproliferative effects of 17β-estradiol" (see page 983, right column, lines 21-24).

It is thus submitted that a person of ordinary skill in the art could not have predicted in view of Ungs' teachings alone or in combination with Collins' or Pitha's that estradiol had the claimed

beneficial effect on reendothelization and vascular endothelial function. These references alone or in combination do not either suggest a specific dosage for achieving this effect.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw this rejection.

DOUBLE PATENTING

Claims 1-4 and 8-23 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 9-10 and 15-33 of co-pending application No. 10/602,934 in view of Ungs.

The Examiner states that "one of ordinary skill in the art would find it obvious to apply the restenosis inhibiting method of the co-pending application for the reendothelization and vascular endothelial function improving, as in the instant claims, with the expectation that the method that inhibits restenosis also improves the vascular endothelial growth and function" (last 5 lines of page 11 of the instant Office Action).

Although the Applicant disagrees and refers the Examiner to above-presented arguments, as support to the fact that restenosis and reendothelization are two independent events that are affected differently by different compounds, a terminal disclaimer is included to accelerate allowance of the present case.

The rejections of the original claims are believed to have been overcome by the present remarks and the introduction of new claims. From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order, and such an action is earnestly solicited.

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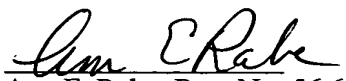
The Commissioner is authorized to charge any fees under 37 CFR §1.17 that may be due on this application to Deposit Account 17-0055. The Commissioner is also authorized to treat this amendment and any future reply in this matter requiring a petition for an extension of time as incorporating a petition for extension of time for the appropriate length of time as provided by 37 CFR §136(a)(3).

Respectfully submitted,

Institut de Cardiologie de Montréal (ICM)

by: Quarles and Brady, LLP

Date: September 29, 2006



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